

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant:	Debatin <i>et al.</i>	Filed via EFS Web April 1, 2008
Title:	SMAC-PEPTIDES AS THERAPEUTICS AGAINST CANCER AND AUTOIMMUNE DISEASES	
Appl. No.:	10/511,037	
§371 Date:	January 19, 2005	
I.A. Filing Date	April 17, 2003	
Examiner:	Hong Sang	
Art Unit:	1643	
Confirmation Number:	6277	

**STATEMENT AND DECLARATION TO SUPPORT FILING AND SUBMISSION OF  
SEQUENCE LISTING BY AMENDMENT IN ACCORDANCE WITH  
37 C.F.R. § 1.57(f)**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Sir:

In connection with a Sequence Listing submitted concurrently herewith for insertion into the captioned specification, the undersigned hereby declares that the material being inserted by amendment is the material previously incorporated by reference and that the amendment contains no new matter.

The sequence listing submitted herewith includes the sequences from GenBank accession numbers disclosed in the captioned application and priority documents EP 02008199.8 and EP 02015499.3. Specifically, the sequence listing includes the Smac polypeptide of GenBank accession no. AAF87716 (SEQ ID NO:1), the polynucleotide encoding the Smac polypeptide as disclosed in GenBank accession no. AF262240 (SEQ ID NO:2), the HIV-1 tat polypeptide of GenBank accession no. CAA45921 (SEQ ID NO:3) and the polynucleotide encoding the HIV-1 Genome of GeneBank accession no. M15654 (SEQ ID NO:4).

The GenBank accession numbers referred to above may be found on page 4, line 15; page 6, lines 9-10; and page 16, line 1 of the International Publication No. WO 03/086470, which corresponds to the present application. Additionally, the GenBank accession numbers AAF87716, AF262240; and CAA45921 may be found in priority document EP 02015499.3 on page 2, line 28; page 6, lines 4-5 and page 12, lines 15-16. Finally, the GenBank accession numbers AAF87716, AF262240; and M15654 may be found in priority document EP 02008199.8 on page 2, line 28; page 6, line 5 and page 15, line 4.

Submitted herewith as Exhibits 1-4 are copies of each of the GenBank entries and their respective sequence revision histories. Genbank accession numbers AAF87716 and AF262240 have never been revised since their original GenBank submission. *See* Exhibits 1-2. GenBank accession numbers CAA45921 and M15654 have been revised, however the version numbers of the sequences have remained the same as indicated on the sequence revision history of each submission. *See* Exhibits 3 and 4. The revisions indicated in the histories for GenBank accession numbers CAA45921 and M15654 do not relate to sequence revisions. A revision of a sequence itself would have changed the version number of the sequence, according to the National Center for Biotechnology Information (NCBI). As such, the undersigned believes that the amendment to add the sequence listing filed herewith does not introduce new matter.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Respectfully submitted,

Date April 1, 2008

FOLEY & LARDNER LLP  
Customer Number: 22428  
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Facsimile: (202) 672-5399



By Michele M. Simkin  
Attorney for Applicant  
Registration No. 34,717

Reg # 54,161

# EXHIBIT 1

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Range: from begin to end Features:  CDD

1: AAF87716. Reports Smac [Homo sapien...[gi:9454219]]

BLINK, Conserved Domains, Links

Features Sequence

LOCUS AAF87716 239 aa linear PRI 26-JUL-2000  
 DEFINITION Smac [Homo sapiens].  
 ACCESSION AAF87716  
 VERSION AAF87716.1 GI:9454219  
 DBSOURCE locus AF262240 accession AF262240.1  
 KEYWORDS .  
 SOURCE Homo sapiens (human)  
 ORGANISM Homo sapiens  
 Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
 Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;  
 Catarrhini; Hominidae; Homo.  
 REFERENCE 1 (residues 1 to 239)  
 AUTHORS Du,C., Fang,M., Li,Y., Li,L. and Wang,X.  
 TITLE Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP inhibition  
 JOURNAL Cell 102 (1), 33-42 (2000)  
 PUBMED 10929711  
 REFERENCE 2 (residues 1 to 239)  
 AUTHORS Du,C., Fang,M., Li,Y. and Wang,X.  
 TITLE Direct Submission  
 JOURNAL Submitted (01-MAY-2000) Howard Hughes Medical Institute and Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235, USA  
 COMMENT Method: conceptual translation supplied by author.  
 FEATURES Location/Qualifiers  
 source 1..239  
 /organism="Homo sapiens"  
 /db\_xref="taxon:9606"  
 Protein 1..239  
 /product="Smac"  
 /function="binds IAPs and neutralizes their inhibition on caspase activation and activity"  
 /name="antagonist of IAPs (inhibitors of apoptosis)"  
 transit peptide 1..55  
 /note="mitochondrial targeting sequence"  
 Region 6..239  
 /region\_name="Smac\_DIABLO"  
 /note="Second Mitochondria-derived Activator of Caspases; pfam09057"  
 /db\_xref="CDD:72475"  
 CDS 1..239  
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## ORIGIN

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121 lgkmnseeded evwqviigar aemtskhqey lklettwmta vglsemaaea ayqtgadqas
181 itarnhiqlv klqveevhql srkaetklae aqieelrqkt qeegeeraes eqeaylred
//
```

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Genome

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## Sequence Revision History

Find (Accessions, GI numbers or Fasta style SeqIds) AAF87716

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### Revision history for AAF87716

Entrez

GI	Version	Update Date	Status
9454219	1	Jul 26 2000 12:05 AM	Live

Accession AAF87716 was first seen at NCBI on Jul 26 2000 12:05 AM

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# EXHIBIT 2

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Display GenBank Show 5 Send to Hide:  sequence  all but gene, CDS and mRNA

Range: from begin to end  Reverse complemented strand Features:  SNP + Refr

1: AF262240. Reports Homo sapiens Smac...[gi:9454218]

Links

Features Sequence

LOCUS AF262240 1358 bp mRNA linear PRI 26-JUL-2000  
 DEFINITION Homo sapiens Smac mRNA, complete cds; nuclear gene for mitochondrial product.  
 ACCESSION AF262240  
 VERSION AF262240.1 GI:9454218  
 KEYWORDS .  
 SOURCE Homo sapiens (human)  
 ORGANISM Homo sapiens Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.  
 REFERENCE 1 (bases 1 to 1358)  
 AUTHORS Du,C., Fang,M., Li,Y., Li,L. and Wang,X.  
 TITLE Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP inhibition  
 JOURNAL Cell 102 (1), 33-42 (2000)  
 PUBMED 10929711  
 REFERENCE 2 (bases 1 to 1358)  
 AUTHORS Du,C., Fang,M., Li,Y. and Wang,X.  
 TITLE Direct Submission  
 JOURNAL Submitted (01-MAY-2000) Howard Hughes Medical Institute and Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235, USA  
 FEATURES Location/Qualifiers  
 source 1..1358 /organism="Homo sapiens"  
 /mol\_type="mRNA"  
 /db\_xref="taxon:9606"  
 CDS 20..739 /function="binds IAPs and neutralizes their inhibition on caspase activation and activity"  
 /note="antagonist of IAPs (inhibitors of apoptosis)"  
 /codon\_start=1  
 /product="Smac"  
 /protein\_id="AAF87716.1"  
 /db\_xref="GI:9454219"  
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 transit peptide 20..184 /note="mitochondrial targeting sequence"

## ORIGIN

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181 gtgtgcgggtt cctattgcac agaaatcaga gcctcattcc ctttagtagtg aagcattgtat
241 gaggagagca gtgtcttgg taacagatag cacctctacc tttctctc agaccacata
301 tgcgttgatt gaagctatta ctgaatatac taaggctgtt tataacctaa cttctcttta
361 ccgacaatat acaagttac ttggggaaaat gaattcagag gaggaagatg aagtgtggca
421 ggtgtatcata ggagccagag ctgagatgac ttcaaaaacac caagagtact tgaagctgga
481 aaccacttgg atgactgcag ttggcttgc agagatggca gcagaagctg catatcaa
541 tggcgcagat caggcctcta taaccgcag gaatcacatt cagcttgta aactgcaggt
601 ggaagaggtg caccagctct cccggaaagc agaaaaccaag ctggcagaag cacagataga
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841 cggcaggtcc tgccctggcc aatcaggcga gacgccttgc tgagctgtga gtgcctcctg
901 tggatgcgg cttgcgttgg acctgggttct tagcccttgg gcactgcacc ctgtttaaca
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1021 ttgccttaccc gggtcagaga gaggagtct tttgttcatg cccttaagtt cagcaactgt
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1141 tggatgcgg gttgtggcag ggggagggga acctgtccag tttgtacat ttctttgtat
1201 gtatttctga tgtgttctct gatctgcccc cactgtccctg tgaggacagc tgaggccaag
1261 gaggtaaaaaa cctattacta ctaagagaag gggtgccagag tggttacctg gtgtctcaaa
1321 caggacttaa catcaacagg acttaacaca gaaaaaaaaa
```

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## Sequence Revision History

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### Revision history for AF262240

[Entrez](#)

GI	Version	Update Date	Status
9454218	1	Jul 26 2000 12:05 AM	Live

Accession AF262240 was first seen at NCBI on Jul 26 2000 12:05 AM

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Range: from begin to end Features:  CDD  Refresh

1: CAA45921. Reports HIV-1 tat [Human ...[gi:60145]] BLink, Conserved Domains, Links

Features Sequence

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LOCUS      CAA45921          86 aa           linear    VRL 20-NOV-1992
DEFINITION HIV-1 tat [Human immunodeficiency virus 1].
ACCESSION  CAA45921
VERSION    CAA45921.1 GI:60145
DBSOURCE   embl accession X64650.1
KEYWORDS
SOURCE     Human immunodeficiency virus 1 (HIV-1)
ORGANISM   Human immunodeficiency virus 1
Viruses; Retro-transcribing viruses; Retroviridae;
Orthoretrovirinae; Lentivirus; Primate lentivirus group.
1 (residues 1 to 86)
REFERENCE
AUTHORS   Siderovski,D.P., Matsuyama,T., Frigerio,E., Chui,S., Min,X.,
Erfle,H., Sumner-Smith,M., Barnett,R.W. and Mak,T.W.
TITLE     Random mutagenesis of the human immunodeficiency virus type-1
trans-activator of transcription (HIV-1 Tat)
JOURNAL   Nucleic Acids Res. 20 (20), 5311-5320 (1992)
PUBMED    1437550
REFERENCE
AUTHORS   Siderovski,D.P.
TITLE     Direct Submission
JOURNAL   Submitted (26-FEB-1992) D.P. Siderovski, Dept of Medical
Biophysics, University of Toronto, 500 Sherbourne Street, Toronto
Ontario M4X 1K9, CANADA
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          /db_xref="taxon:11676"
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Region
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retroviral Tat protein binds to the Tar RNA. This
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CDS
ORIGIN

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61 gsqthqvsls kqptsqsrqd ptgpke  
//

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## Sequence Revision History

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GI	Version	Update Date	Status	I	II
60145	1	Oct 20 2006 8:41 AM	Live	<input checked="" type="radio"/>	<input type="radio"/>
60145	1	Aug 8 2003 11:42 PM	Dead	<input type="radio"/>	<input checked="" type="radio"/>
60145	1	Oct 19 2002 2:32 PM	Dead	<input type="radio"/>	<input type="radio"/>
60145	1	Mar 8 1999 10:26 PM	Dead	<input type="radio"/>	<input type="radio"/>
60145	1	May 25 1995 12:46 PM	Dead	<input type="radio"/>	<input type="radio"/>
60145	1	Dec 1 1994 11:51 AM	Dead	<input type="radio"/>	<input type="radio"/>
60145	1	Sep 1 1993 8:12 PM	Dead	<input type="radio"/>	<input type="radio"/>
60145	1	Apr 21 1993 5:17 PM	Dead	<input type="radio"/>	<input type="radio"/>

Accession CAA45921 was first seen at NCBI on Apr 21 1993 5:17 PM

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# EXHIBIT 4

 NCBI

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Books

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Display GenBank Show 5 Send to Hide:  sequence  all but gene, CDS and mRNA

Range: from begin to end Reverse complemented strand Features:  Refresh

1: M15654. Reports Human immunodefici...[gi:326383]

Links

Comment Features Sequence

**LOCUS** HIVBH102 8932 bp ss-RNA linear VRL 02-AUG-2006  
**DEFINITION** Human immunodeficiency virus type 1, isolate BH10, genome.  
**ACCESSION** M15654 K02008 K02009 K02010  
**VERSION** M15654.1 GI:326383  
**KEYWORDS** TAR region; acquired immune deficiency syndrome; env protein; gag protein; long terminal repeat (LTR); pol protein; polyprotein; proviral gene; reverse transcriptase; transactivator.  
**SEGMENT** 2 of 2  
**SOURCE**  
**ORGANISM** Human immunodeficiency virus 1 (HIV-1)  
 Viruses; Retro-transcribing viruses; Retroviridae;  
 Orthoretrovirinae; Lentivirus; Primate lentivirus group.  
**REFERENCE**  
**AUTHORS** Wong-Staal,F., Gallo,R.C., Chang,N.T., Ghrayeb,J., Papas,T.S., Lautenberger,J.A., Pearson,M.L., Petteway,S.R.Jr., Ivanoff,L., Baumeister,K., Whitehorn,E.A., Rafalski,J.A., Doran,E.R., Josephs,S.J., Starcich,B., Livak,K.J., Patarca,R., Haseltine,W.A. and Ratner,L.  
**TITLE** Complete nucleotide sequence of the AIDS virus, HTLV-III  
**JOURNAL** Nature 313 (6000), 277-284 (1985)  
**PUBMED** 2578615  
**REFERENCE** 2 (bases 1 to 8932)  
**AUTHORS** van Beveren,C.P., Coffin,J. and Hughes,S.  
**TITLE** Appendix B: HTLV-3 genome  
**JOURNAL** (in) Weiss,R.L., Teich,N., Varmus,H. and Coffin,J. (Eds.); RNA TUMOR VIRUSES, MOLECULAR BIOLOGY OF TUMOR VIRUSES, SECOND EDITION, 2;  
 Cold Spring Harbor Laboratory, CSH, NY (1985)  
**REFERENCE** 3 (sites)  
**AUTHORS** Hostomsky,Z., Hostomska,Z., Hudson,G.O., Moomaw,E.W. and Nodes,B.R.  
**TITLE** Reconstitution in vitro of RNase H activity by using purified N-terminal and C-terminal domains of human immunodeficiency virus type 1 reverse transcriptase  
**JOURNAL** Proc. Natl. Acad. Sci. U.S.A. 88 (4), 1148-1152 (1991)  
**PUBMED** 1705027  
**COMMENT** Original source text: Human immunodeficiency virus type 1 (HIV-1) proviral DNA clone BH10.  
 [(in) Weiss,R., Teich,N., Varmus,H. and Coffin,J. (Eds.); RNA Tumor Viruses, Molecular review; bases 1 to 8932.  
 The BH10 sequence differs from BH8 and BH5 by 0.9% in the coding regions and 1.8% in the noncoding regions, and the authors of [1] believe that these are stable variants.  
 The HTLV-III genome encodes at least seven proteins: gag, pol, env,

tat, trs, 27K antigen and the sor 23K product. The 3' ORF (positions 8153-8773) is truncated in BH10 (stop codon at positions 8522-8524), but reads through in BH8 and other sequences to yield what is now called the 27K antigen.

The mechanism for pol gene translation has not been elucidated: a gag-pol fusion protein is possible; splicing or frameshift have not been ruled out. The viral protease would be determined by the region in question.

The Tat protein (trans-activator protein, approximately 14 kb) is an effector of an autostimulatory pathway through interaction with a positive control element, the trans-activating responsive sequence, TAR. Tat seems to be a transcriptional control molecule in HTLV-I, but is both that and a post-transcriptional regulatory molecule in HTLV-III. Deletion mutants in the tat gene are incapable of prolific replication and exhibit no cytopathic effects in T4+ cell lines.

In addition to the

9.4 kb genomic mRNA, subgenomic mRNAs of 7.4, 5.5, 5.0, 4.3, 2.0 and 1.8 kb have been detected.

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intron	66..5135 /note="tat, rev, nef subgenomic mRNA intron 1"
gene	112..1650 /gene="gag"
CDS	112..1650 /gene="gag" /codon_start=1 /product="gag polyprotein precursor" /protein_id="AAA44201.1" /db_xref="GI:326388" /translation="MGARASVLSGGELDRWEKIRLRPGGKKYKLKHIVWASRELERF AVNPGLLETSEGCRQILGQLQPSSLQTGSEELRSLYNTVATLYCVHQRIEIKDTKEALD KIEEEQNKSKKAAQQAAADTGHSSQVSQNYPIVQVNIQGQMVKHQAISPTLN AWVKVVEEKAFSPEVIPMFALSEGATPQDLMNTLNTVGGHQAMQMLKETINE EAAEWDRVHPVHAGPIAPGQMREPRGSDIAGTTSTLQEIQGWM TNPPIPVGEIYKRWIILGLNKIVRMYSPTSILD IQRGPKEPFRDYVDRFYKTLRAEQASQEVKN WMTETLLVQNANPDCKTIL KALGPAATLEEMMTACQGVGGPGHKARV LAEAMSQVTNTATIMMQRGNFRNQR MVKCFCNGKEGHTARNCRAPRK KKGCWKCGKEGHQMKDTERQANFLGKI WPSYKGRPGNFLQSR PEPTAPPFLQSRPEPTAPPEESFRSG VETTPPKQEPIDKELYPLTS LRLSLFGNDPSSQ"
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 KGGIGGYSAGERIVDIIATDIQTKELOKQITKIQNFRVYRDSRNPLWKGPALKLWKG  
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gene

4399..4977

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CDS

4399..4977

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gene

4917..5153

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CDS

4917..5153

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CDS

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intron

5404..7733

/note="tat, rev, nef subgenomic mRNA intron 2"

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repeat region 8894..>8932
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8881 ttttgcctgt actgggtctc tctggttaga ccagatctga gcctgggagc tc

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Aug 28 2007 16:53:42



Nucleotide

Protein

Genome

Structure

PMC

Taxonomy

OMIM

G

## Sequence Revision History

**Find (Accessions, GI numbers or Fasta style Seqlds) M15654**

About Entrez

Show difference between I and II as GenBank/GenPept

Entrez

### Revision history for M15654

GI	Version	Update Date	Status	I	II
326383	1	Aug 2 2006 2:51 PM	Live	<input checked="" type="radio"/>	<input type="radio"/>
326383	1	Oct 4 1994 9:13 AM	Dead	<input type="radio"/>	<input checked="" type="radio"/>
326383	1	Aug 2 1993 8:33 PM	Dead	<input type="radio"/>	<input type="radio"/>

Accession M15654 was first seen at NCBI on Aug 2 1993 8:33 PM

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Entrez Gene provides gene-specific data for multiple taxa

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Entrez Gene

Clusters of orthologous groups

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